UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM
7/2/2007

SUBJECT: **The Mode of Action and Human Relevance of HPPD-Inhibiting Herbicides (D 341612)**

FROM: **Hazard Science Policy Council**
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TO: PV Shah (Acting Branch Chief, RAB1)
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PURPOSE OF MEETING:

The HED HASPOC met on June 28, 2007 to discuss (i) whether HPPD-inhibiting pesticides shared a common effect and common mechanism of toxicity; (ii) species differences in the animal toxicity studies, and species differences in the expression of TAT (tyrosine aminotransferase), (iii) the human experience with genetic disorders of tyrosinemia and treatment with HPPD inhibiting drugs (e.g., Nitisinone); and (iv) whether the rat ocular toxicity is an appropriate model in our health risk assessments as a regulatory endpoint.

HASPOC agreed that there was evidence of an association of HPPD inhibition leading to induced tyrosinemia (elevated plasma tyrosine levels) and ocular effects. However, because humans have an efficient metabolic process to handle excess plasma tyrosine levels and given the clinical experience with HPPD-inhibiting drugs, it is unlikely that exposure to pesticide residues will result in tyrosinemia-related toxicity in humans as observed in the rat (the susceptible species). **Accordingly, although HPPD inhibiting-herbicides may share a common mode of action, exposure to these herbicides are unlikely to induce adverse health outcomes in humans. Thus, there is not a likely human health impact to indicate the need for a cumulative risk assessment.** OPP should depart from this science policy where new facts or circumstances warrant, however.

The following boilerplate language is suggested for the HPPD-Inhibiting herbicides.

Pesticide X belongs to a class of herbicides that inhibit the liver enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD), which is involved in the catabolism (metabolic breakdown) of tyrosine (an amino acid derived from proteins in the diet). Inhibition of HPPD can result in elevated tyrosine levels in the blood, a condition called tyrosinemia. HPPD-inhibiting herbicides have been found to cause a number of toxicities in laboratory animal studies including ocular, developmental, liver and kidney effects. Of these toxicities, it is the ocular effect (corneal opacity) that is highly correlated with the elevated blood tyrosine levels. In fact, rats dosed with tyrosine alone show ocular opacities similar to those seen with HPPD inhibitors. Although the other toxicities may be associated with chemically-induced tyrosinemia, other mechanisms may also be involved.

There are marked differences among species in the ocular toxicity associated with inhibition of HPPD. Ocular effects following treatment with HPPD inhibitor herbicides are seen in the rat but not in the mouse. Monkeys also seem to be recalcitrant to the ocular toxicity induced by HPPD inhibition. The explanation of this species-specific response in ocular opacity is related to the species differences in the clearance of tyrosine. A metabolic pathway exists to remove tyrosine from the blood that involves a liver enzyme called tyrosine aminotransferase (TAT). In contrast to rats where ocular toxicity is observed following exposure to HPPD-inhibiting herbicides, mice and humans are unlikely to achieve the levels of plasma tyrosine necessary to produce ocular opacities because the activity of TAT in these species is much greater compared to rats. Thus, humans and mice have a highly effective metabolic process for handling excess tyrosine.

HPPD inhibitors (*e.g.,* Nitisinone) are used as an effective therapeutic agent to treat patients suffering from rare genetic diseases of tyrosine catabolism. Treatment starts in childhood but is often sustained throughout patients lifetime. The human experience indicates that a therapeutic dose (1 mg/kg/day dose) of Nitisinone has an excellent safety record in infants, children and adults and that serious adverse health outcomes have not been observed in a population followed for approximately a decade. Rarely, ocular effects are seen in patients with high plasma tyrosine levels; however these effects are transient and can be readily reversed upon adherence to a restricted protein diet. This indicates that an HPPD inhibitor in it of itself cannot easily overwhelm the tyrosine-clearance mechanism in humans.

Therefore, exposure to environmental residues of HPPD-inhibiting herbicides are unlikely to result in the high blood levels of tyrosine and ocular toxicity in humans due to an efficient metabolic process to handle excess tyrosine. Single chemical risk assessments for which the hazard endpoint selected is from a rat toxicity

study and the effect observed is ocular opacity due to tyrosinemia should be considered worst case.